II. REMARKS

Preliminary Remarks

Claims 1-17 were previously canceled. Claims 18 and 24 are amended, claims 19-23 and 25-47 are canceled, and new claims 48-55 are added.

Claims 18 and 24 are amended to specify that the non-proteinaceous agent is the agent of claim 20 and the disease-associated protein is SAP, in accord with the telephonic election of February 16, 2005, in response to a new restriction requirement communicated by the examiner by telephone on January 26, 2005.

Claims 19-23 and 25-47, directed to non-elected subject matter or to subject matter added to claims 18 and 24 in accord with the election of February 16, 2005, are canceled.

New claims 48 and 52 are directed to the method of claims 18 and 24, respectively, wherein the specified D-proline is administered orally with a dosage of 50 to 500 mg/per day, as described on page 8 (3rd to last line).

New claims 49 to 54 are directed to the method of claims 18 and 24, respectively, wherein the specified D-proline is administered by injection with a dosage of 0.05 to 6 mg/kg/day, or 0.1 to 6 mg/kg/day, or 0.25 to 6 mg/kg/day. Support for these claims is found on page 14 (6th to last line), where injected dosage as low as 0.05 mg/kg/day is shown to be effective, and on page 16 (lines 10-11) and page 21 (line 12), where injected dosages of 0.1 or 0.25 to 6 mg/kg/day are described as being effective.

Patentability Remarks

Rejections under 35 U.S.C. §103(a)

Claims 18 and 24 were rejected under 35 U.S.C. §103(a) as allegedly being obvious in view of Hertel et al., considered together with van Kessel et al.

Attached hereto is a declaration under 37 C.F.R.. §1.132 by the inventor, Professor Mark B. Pepys, a prominent scientist in the field of investigating and developing therapies relating to SAP and amyloidosis-associated diseases, which identifies scientific reasons why the cited references would not have motivated one of ordinary skill in the art at the time the invention was made to use the claimed method, or to expect that the claimed method could be practiced successfully. In the attached declaration, Dr. Pepys declares that prior to his discovery of the claimed invention, there was no precedent for a small molecule drug (such as the elected agent) that **specifically** targets a circulating plasma protein such as SAP and causes its rapid clearance from the circulation. No prior art even remotely suggested this completely novel mechanism of drug action. As further evidence of the novel and non-obvious character of this new pharmacological mechanism of drug action, which is the basis

of the claimed invention, Dr. Pepys cites an article published in *Chemical and Engineering News*, a journal of the American Chemical Society, which identifies the invention as one of the highlights in the field of medicinal chemistry for the year 2002 (*Chem. Eng. News*, 2002, 80:37-38), and an article in *Nature* by Leslie Iversen, an eminent neuropharmacologist, which described the work corresponding to the claimed invention as "a new pharmacological approach to treating human amyloid diseases;" and stated that "this new approach offers great promise for treating both peripheral amyloid disorders and possibly, Alzheimer's disease." (Iversen, "Amyloid diseases: Small drugs lead the attack," *Nature*, 2002, 414:231-233). Copies of both articles were submitted with the response filed on November 29, 2004.

As discussed in the attached declaration, the applicant respectfully takes issue with the rejection of the claims as being unpatentable in view of Hertel et al. and van Kessel et al. The examiner described Hertel et al. as having taught administering (R)-1-[6-(R)-2-Carboxypyrrolidin-l-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid (the elected agent) to a patient in order to treat diseases associated with amyloidosis such as Alzheimer's disease, and further stated that Hertel et al. taught that "the compounds administered are used to prevent the interaction of SAP with amyloid fibrils." The examiner further stated that Hertel et al. did not teach monitoring the clearance of SAP from the patient's plasma, but alleged that it would have been obvious to monitor the clearance of SAP from the patient's plasma, because van Kessel et al. taught quantification of the concentration of SAP. See pages 3-4 of the official action.

The applicant respectfully disagrees with the examiner's contention that Hertel et al. taught administering the elected agent to a patient in order to treat diseases associated with amyloidosis such as Alzheimer's disease. The elected agent is one of over a hundred D-proline derivatives that Hertel et al. disclosed and described as being capable of inhibiting the binding of SAP to amyloid fiber. Hertel et al. provided no experimental evidence showing that the elected compound or any of the other disclosed compounds were actually capable of conferring therapeutic benefit to a patient with a disease associated with amyloidosis such as Alzheimer's disease. One of ordinary skill in the art at the time the invention was made would have recognized that *in vivo* testing is generally needed to determine if a new compound is capable of conferring therapeutic benefit. Therefore, one of ordinary skill in the art would reasonably have regarded Hertel et al. as having disclosed a large number of D-proline derivatives, including the elected compound, that inhibit the binding of SAP to amyloid fiber and have undetermined activity as therapeutic agents.

The applicant also respectfully disagrees with the examiner's contention that one of ordinary skill in the art would have been motivated by van Kessel et al. to monitor and quantify the concentration of SAP in a patients plasma, following administration of the elected compound according to Hertel et al. Van Kessel et al. taught that SAP is capable of binding to endotoxin

(col. 1, lines 47 to 49), and proposed that SAP can bind to LPS (endotoxin) and neutralize its biological activity (col. 3, lines 50 to 51). The reference hypothesized that chronic bacterial infections and particularly LPS contribute to the development of Alzheimer's disease (col. 3, lines 60 to 64), and that SAP and fragments derived from SAP with a strong LPS-binding and neutralizing action can therefore be of importance in eliminating the part played by LPS in the development of Alzheimer's disease (col. 4, lines 39 to 43). Van Kessel et al. proposed that SAP and/or fragments thereof should be administered to patients in order to treat or prevent Alzheimer's disease. Moreover, van Kessel et al. did not describe or suggest quantifying the concentration of SAP in a patient's blood or plasma. In column 5, lines 1 to 20, van Kessel et al. taught that SAP and/or fragments thereof can also be used for the diagnosis of infection with gram negative bacteria or sepsis. However, it is the presence of endotoxin in blood or blood fractions such as serum or plasma, not SAP, that is to be measured. SAP is bound to a carrier such as a microtitre plate, column, membrane or beads (column 5, lines 19 and 20) and the endotoxin is assayed from the blood sample. Binding between endotoxin and SAP is measured in order to quantify endotoxin in the blood, and not to measure the concentration of SAP.

The method taught by Van Kessel et al. would increase a patient's circulating SAP concentration, which is exactly the opposite of the effect of the claimed invention, which rapidly depletes SAP from the circulation to provide therapeutic benefit to patients with amyloidosis of all types, and amyloid-associated diseases such as Alzheimer's disease. The Hertel et al. and van Kessel et al. references are also directed to conflicting purposes - Hertel et al. teaches inhibiting SAP binding activity, whereas van Kessel et al. teaches administering an LPS-binding form of SAP. Neither of the cited references described clearance of SAP from plasma or suggested monitoring SAP levels in plasma. On the other hand, monitoring the concentration of circulating SAP is a part of the proper use of the claimed invention to ensure that SAP depletion is taking place. In view of the foregoing, Hertel et al taken with van Kessel et al. would not have suggested the claimed method to one of ordinary skill in the art at the time the invention was made. Furthermore, the cited references could not have provided one of ordinary skill in the art with any basis for having a reasonable expectation that the claimed method would operate successfully; *i.e.*, that SAP could be depleted from the plasma of a patient in need of such treatment by administration of the elected agent, and that the clearance of the SAP from the patient's plasma following such treatment could be successfully monitored.

In view of the foregoing and Professor Pepys's declaration, withdrawal of the rejection of the pending claims under 35 U.S.C. §103(a) as allegedly being unpatentable in view of Hertel et al., taken with van Kessel et al., is therefore respectfully requested.

III. CONCLUSION

It is respectfully submitted that the present application is in condition for allowance and a notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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